

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
2 September 2004 (02.09.2004)

PCT

(10) International Publication Number
WO 2004/074285 A1

- (51) International Patent Classification⁷: **C07D 471/04**, (74) Agents: **YAGI, Hidehito et al.**; Aoba International Patent Office, Daiichi-Okouchi Bldg. 6F, 1-10-6, Kajicho, Chiyoda-ku, Tokyo 101-0044 (JP).
- (21) International Application Number: **PCT/JP2004/002087**
- (22) International Filing Date: 23 February 2004 (23.02.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
2003-046335 24 February 2003 (24.02.2003) JP
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/074285 A1

(54) Title: THE ENANTIOMER OF TENATOPRAZOLE AND THE USE THEREOF IN THERAPY

(57) Abstract: This invention relates to optically active substances of tenatoprazole, (+) and (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine. The compound and pharmaceutical compositions thereof are useful for anti-ulcer agent.

DESCRIPTION

The Enantiomer of Tenatoprazole and the use thereof in therapy

Field of the Invention

The present invention concerns tenatoprazole, and more particularly an enantiomer of tenatoprazole, a method for its preparation and its use in human or veterinary therapy.

Background Art

Tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl)methyl} sulfinyl} imidazo-[4,5-b] pyridine, is described in Patent No. EP 254,588. It belongs to the group of drugs considered as proton pump inhibitors, which inhibit the secretion of gastric acid and are useful in the treatment of gastric and duodenal ulcers. It can also be used to treat gastro-oesophageal reflux, digestive bleeding and dyspepsia, because of its relatively long elimination half-life, as described in the application for French patent No. FR 02. 13113.

The first known derivative of this series of proton pump inhibitors was omeprazole, described in Patent No. EP 001,529, which is endowed with properties which inhibit the secretion of gastric acid and is widely employed as an anti-ulcerative in human therapeutics.

In addition to omeprazole, other proton pump inhibitors are well known, and particular mention can be made of rabeprazole, pantoprazole and lansoprazole, which all exhibit structural analogy and lansoprazole, which all exhibit structural analogy and belong to the group of pyridinyl methyl sulfinyl benzimidazoles. These compounds are sulfoxides presenting with asymmetry at the level of the sulphur atom, and therefore generally take the form of a racemic mixture of two enantiomers.

Like omeprazole and other sulfoxide with an analogue structure, tenatoprazole has an asymmetric structure and may therefore be present in the form of a racemic mixture or of its enantiomers. Thus it may exist in the form of its two enantiomers with R and S configurations, or (+) or (-), respectively.

Recent studies have shown that, unlike all the other proton pump inhibitors such as, for example, omeprazole or lansoprazole, and unexpectedly, tenatoprazole is endowed with a markedly prolonged duration of action, resulting from a plasma half-life which is about seven times longer. Thus the clinical data collected have shown that tenatoprazole enables a degree of symptom relief and healing of gastric lesions which is superior to that achieved by other drugs

belonging to the same therapeutic category of proton pump inhibitors, which thus allows its effective use in the treatment of atypical and oesophageal symptoms of gastro-oesophageal reflux, digestive bleeding and dyspepsia, as indicated above.

Studies performed by the application have made it possible to show that the two enantiomers contribute differently to the properties of tenatoprazole, and that the two enantiomers, (+) and (-) exhibit significantly different pharmacokinetic properties. Thus it is possible to prepare medicinal products with specific activity by isolating the enantiomers, and these enantiomers themselves exhibit a different pharmacokinetic profile from that of the known racemic mixture. It then becomes possible to use each of these enantiomers more effectively in precise indications for the treatment of perfectly identified pathologies.

Summary of the Invention

Thus the aim of the present invention is the followings:

1. The compound (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts.
2. A method for the preparation of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, comprising column chromatography on racemic mixture.
3. The method according to the above 2, wherein the column chromatography is chiral or HPLC chromatography.
4. The method according to the above 2 or 3, wherein (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine is salfied by the action of basic mineral reagents comprising alkaline or earth-alkaline counter-ion.
5. A pharmaceutical composition comprising (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, and one more pharmaceutically acceptable excipients or substances.
6. The pharmaceutical composition according to the above 5, wherein (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine takes the form of an alikale or earth-alkaline metal salt.
7. The pharmaceutical composition according to the above 5, wherein (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine takes the form of a sodium, potassium, lithium, magnesium or calcium salt.
8. The pharmaceutical composition according to the above 5 to 7, comprising

unitary doses containing from about 10 to about 80 mg of active ingredient.

9. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies.

10. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies wherein the inhibition of acid secretion must be strong and prolonged.

11. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine for the treatment of Barrett's syndrome, atypical and oesophageal symptoms of gastro-oesophageal reflux, and digestive bleeding refractory to other proton pump inhibitors.

12. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies, gastro-oesophageal reflux, and digestive bleeding, in patients receiving multiple drug therapy.

13. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine in combination with one or more antibiotics in the manufacture of a medicinal product for the treatment of duodenal ulcer resulting from an infection by Helicobacter pylori.

14. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine in the manufacture of a medicinal product displaying improved pharmacokinetic properties.

15. The compound (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts.

16. A method for the preparation of (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, comprising that chloroform is used as a solvent and 5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] thio} imidazo-[4,5-b] pyridine is subjected to asymmetric oxidation.

17. The method according to the above 16, wherein optically active binaphthol, titanium tetrakisopropoxide, water and tert-butylhydroperoxide are used.

18. A pharmaceutical composition comprising (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, and one or more pharmaceutically acceptable excipients or substances.

19. The pharmaceutical composition according to the above 18, wherein (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine takes the form of an alkali or earth-alkaline

metal salt.

20. The pharmaceutical composition according to the above 18, wherein (+)-tenatoprazole, or (+)-5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine takes the form of a sodium, potassium, lithium, magnesium or calcium salt.
21. The use of (+)-tenatoprazole, or (+)-5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts for the treatment of digestive pathologies.
22. The use of (+)-tenatoprazole, or (+)-5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine for the treatment of Barrett's syndrome, atypical and oesophageal symptoms of gastro-oesophageal reflux, and digestive bleeding refractory to other proton pump inhibitors.
23. The use of (+)-tenatoprazole, or (+)-5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies, gastro-oesophageal reflux, and digestive bleeding, in patients receiving multiple drug therapy.

Best Mode for carrying out the Invention

The (-) enantiomer of tenetoprazole can be used in the form of a salt, including an alkaline or earth-alkaline metal salt, and, for example, in the form of a sodium, potassium, lithium, magnesium or calcium salt. These salts can be obtained from the (-) enantiomer of tenatoprazole which has previously been isolated by salification, according to the standard method of the technique, for example by the action of basic mineral reagents comprising alkaline or earth-alkaline counter-ions.

The (-) enantiomer complying with the present invention can be obtained in a pure optical form simply from the racemic mixture, using any appropriate method of separation, and more particularly by preparative column chromatography, for example, chiral or HPLC chromatography. "Pure optical form" implies that the (-) enantiomer is substantially exempt of the (+) enantiomer, or only contains traces of it. If relevant, salification with a base is then performed in an appropriate solvent, to form a salt, and particularly an alkaline or earth-alkaline metal salt.

The principle of the chiral chromatography method is based on the difference in affinity existing between the (+) and (-) enantiomers and the chiral selector of the stationary phase. This method enables the separation of enantiomers with a satisfactory yield.

The (-) enantiomer of tenatoprazole corresponds to (-)-5-methoxy-2-{[(4-

methoxy-3,5-dimethyl-2-pyridyl) methyl] sulfinyl} imidazo-[4,5-b] pyridine, or (-)-tenatoprazole. This form can be determined by optical rotation measurements using standard technique.

For example, it is possible to prepare a solution of the desired enantiomer at 0.25% (50 mg of a sample per 20 ml of solvent) dissolved in DMF or acetonitrile, and using a polarimeter of a commonly employed type (Jobin Yvon). Thus, the angle of optical rotation of (-)-tenatoprazole is laevogyre in dimethylformamide and acetonitrile, and its melting point is 130 °C (decomposition).

The racemic mixture used as the starting material can be obtained using known processes, for example according to the procedure described in Patent No. EP 254,588. Thus, it can be prepared using an oxidising agent, such as perbenzoic acid, to treat the corresponding sulfide arising from the condensation of a thiol and a pyridine, preferably in the presence of a base such as potassium hydroxide in an appropriate solvent, for example, ethanol, under heating.

The method used to separate enantiomers from the racemic mixture by high performance liquid chromatography (HPLC) makes it possible to isolate the (-) enantiomer with excellent purity (chiral purity: min. 98.8% of the surface area).

Unexpectedly, studies performed on the enantiomer prepared as above have demonstrated that it is endowed with pharmacokinetic properties which are fundamentally different from those of standard proton pump inhibitors, and of racemic tenatoprazole, thus suggesting that it could be used in specific indications.

Thus the racemic mixture and the (-) isomer of tenatoprazole differ significantly in terms of their pharmacokinetic properties, as shown by the studies described below. This characteristic is essential, as it will allow the availability to clinicians of a medicinal product specifically adapted to the effective treatment of determined pathologies.

More particularly, the different pharmacokinetic parameters displayed, and notably the $AUC_{0-\infty}$ (area under the curve) and $t_{1/2}$ (elimination half-life), some subjects were genotyped in order to identify the type of metaboliser, slow or rapid, to which they belonged.

In parallel, a chiral pharmacokinetic study was conducted to assess the preponderance of the pharmacokinetic characteristics of the (-) isomer in the pharmacokinetics of racemic tenatoprazole.

As a general rule, the main problem encountered regarding the metabolism of proton pump inhibitors is that they are mostly metabolised by cytochrome 2C19, which is controlled by chromosome 10, and they thus exhibit

genetic polymorphism, i.e. activity which varies as a function of the type of patient population. This results in variable plasma levels and susceptibility to possibly harmful drug interactions, depending on the individuals concerned.

It seems clear that homozygote subjects with a mutation on exon 5, giving rise to the CYP2C19*2/*2 genotype, exhibit pharmacokinetic characteristics which differ totally from those seen in the standard population. These subjects have a very weak metabolic activity concerning CYP2C19, which is responsible for the metabolism of tenatoprazole. Analysis of the plasma after chiral separation has shown that these subjects displayed a highly significant increase in the (+) isomer when compared with the (-) isomer. These subjects are qualified as slow metabolisers.

Conversely, subjects who are rapid metabolisers, characterised by the CYP2C19*1/*1 genotype, display a higher concentration of the (-) isomer than of the (+) isomer.

Thus, the (+) isomer is metabolised via one preponderant pathway, CYP2C19, while the (-) isomer is metabolised by two pathways, i.e. CYP2C19 and CYP3A4.

These observations have led to the proposal of isolating and administering a single isomer, the (-) isomer, which would have the following advantages:

- a reduction in between-subject variations, hence a better use of the product and a more homogenous response to treatment in all patients,
- improved impregnation of the product, because the rate of elimination is slower and the mean residence time in the body (MRT) is longer,
- a reduction in the number of drug interactions with potentially concomitant medications. Indeed, the (-) isomer is metabolised via two pathways, cytochromes 2C19 and 3A4, which can compensate for any deficiency or blockade of cytochrome 2C19,
- ease of use in all types of patients, whether they are slow or rapid metabolisers. Indeed, the (-) isomer in a slow metaboliser will be metabolised by CYP3A4, thus making it possible to achieve uniform pharmacokinetic parameters whatever the patients, whether they are slow or rapid metabolisers.

Furthermore, isolation of the (-) enantiomer has made it possible to determine a pharmacokinetic profile which differs from that of the racemic mixture, and notably a mean plasma half-life of between about 10 and 12 hours for the (-) enantiomer, at doses of between 20 mg and 80 mg. In contrast, the racemic compound is endowed with a mean plasma half-life of approximately 7 hours at a dose of 20 mg and 9 hours at a dose of 80 mg.

These significantly different properties, in addition to the pharmacological properties found with the racemic mixture, and well known for the pharmacotherapeutic category of proton pump inhibitors (and notably the inhibitory activity of H⁺-K⁺-ATPase pumps on gastric secretion), show that the (-) enantiomer of tenatoprazole can be used to advantage in the treatment of digestive pathologies where it is necessary to obtain a strong and prolonged inhibition of acid secretion. This is the case in Barrett's syndrome, which causes pre-cancerous damage linked to gastro-oesophageal reflux, where the risk of oesophageal adenocarcinoma is directly proportional to the incidence, severity and duration of gastro-oesophageal reflux episodes.

The (-) enantiomer of tenatoprazole is also suitable for the treatment of Zollinger-Ellison syndrome and other syndromes involving acid hypersecretion, the treatment of atypical and oesophageal symptoms of gastro-oesophageal reflux, digestive bleeding refractory to other proton pump inhibitors and treatment of these diseases in patients receiving multiple drug therapy, particularly those receiving treatment which involved the administration of several drugs, and especially elderly patients, with the aim of preventing incidents associated with a drug interaction.

The (-) enantiomer of tenatoprazole can also be used, preferably in combination with one or more antibiotics, to treat ulcers in the event of Helicobacter pylori infection, and notably to eradicate Helicobacter pylori to favour healing of the duodenal ulcer and prevent any recurrence.

The (-) enantiomer of tenatoprazole, in the treatment of the pathologies listed above, and most particularly in the treatment of Barrett's and Zollinger-Ellison syndromes and of gastro-oesophageal reflux and digestive bleeding, can be administered in standard forms adapted to the method of administration chosen, for example via the oral parenteral routes, and preferably via the oral or intravenous routes.

For example, it is possible to use tablet or capsule formulations containing the (-) enantiomer of tenatoprazole as the active substance, or oral solution or emulsions or solutions for parenteral administration containing a tenatoprazole can be chosen, for example, from amongst sodium, potassium, lithium, magnesium or calcium salts.

As an example, an appropriate formulation for tablets containing 20 mg of the (-) isomer of tenatoprazole in combination with pharmaceutically-acceptable substrates and excipients, is shown below:

(-) tenatoprazole	30.0mg
lactose	40.0mg
aluminium hydroxide	17.5mg
hydroxypropyl cellulose	8.0mg
Talc	4.5mg
titanium dioxide	5.0mg
magnesium stearate	20.0mg
standard excipients qs	160.0mg

An example of a formulation for a size 2, gastro-resistant enteric capsule (capsule shell made of acetophthalate, polyvinylpyrrolidone derivatives and acrylic resins), containing 40 mg the (-) isomer of tenatoprazole is shown below:

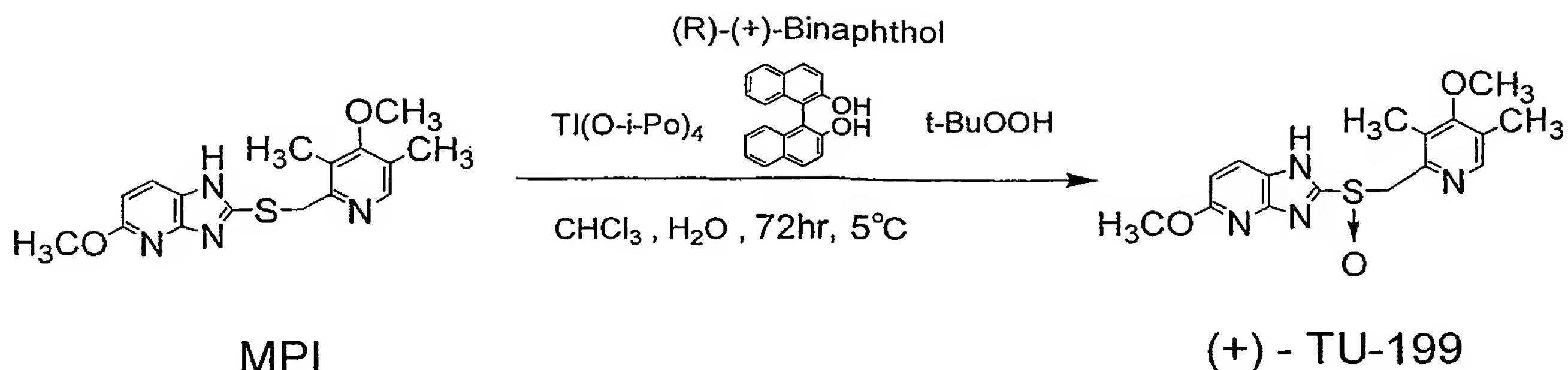
(-)-tenatoprazole	40mg
lactose	200.0mg
magnesium stearate	10.0mg

The dosage is determined by the practitioner as a function of the patient's state and the severity of the condition. It is generally between 10 and 120 mg, and preferably between 20 and 40 mg of the (-)-enantiomer of tenatoprazole, per day. For example, it can be administered at a rate of one intake of 1 or 2 unit doses, (e.g. tablets), each containing 10 to 80 mg, and preferably 20 to 40 mg, of the active substance per day, for a period of time which can range from 4 to 12 weeks, in the context of initial or maintenance therapy. In the case of a pediatric form adapted for use in young children, for example, in the form of an oral solution, the unit dose can be lower, for example, 2 or 5 mg. In the case of severe disorders, it may be effective to administer the medicinal product in the first instance via the intravenous route, and subsequently via the oral route. The invention also has the advantage of permitting effective, sequential treatment with the administration of a single tablet containing 40 mg or 80 mg, per week.

One of the advantages of the present invention is that it allows treatment of the pathologies referred to above with a dosage limited to a single dose of medication per day, including in the treatment of duodenal ulcer resulting from *Helicobacter pylori* infection, unlike standard drugs, including standard proton pump inhibitors, which require two daily doses.

The aim of the present invention is also the (+) configuration enantiomer of the tenatoprazole and its use in human or veterinary therapeutics.

For example, the (+) enantiomer of tenatoprazole can be obtained by using chloroform, an industrially acceptable solvent, in accordance with the method proposed by Umemura et al. (J. Org. Chem. 1993, 58, 4592) as follows:



The invention provides selectivity of asymmetric oxidation at approx. 80%ee whereas the method by Uemura et al., using carbon tetrachloride as a solvent provides optically active substances at a lower purity (refer to Table 1 below).

[Table 1]

Solvent	(+)- tenatoprazole selectivity (%ee)
Chloroform	82
Methylene chloride	6
Carbon tetrachloride	15
THF	14
Ethyl acetate	12

The method described in the invention is able to form (+)-tenatoprazole by using binaphthol (R) whereas (-) tenatoprazole by using binaphthol (S).

Alkali metal salts of the (+) enantiomer of tenatoprazole of the invention, or (+)-5-methoxy-2-{(4-methoxy-3,5-dimethyl-2-pyridyl)methyl}sulfanyl}-1H-imidazo[4,5-b]pyridine indicated by the structural formula include inorganic compounds such as sodium and potassium. Alkali metal salts to be used in the invention are pharmaceutical grades.

Since the compound with the foregoing structure and their alkali metal salts may be present in a form of hydrate or solvate, these hydrates and solvates are also included in the active ingredients of the invention.

The (+) enantiomer of tenatoprazole can be administered and formulated in the same ways as that of (-) enantiomer of tenatoprazole, as aforementioned.

As example of the preparation of the (-) and (+) enantiomer of tenatoprazole is described below in order to illustrate the present invention.

Examples

Example 1 (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine

The conditions for preparative chromatography, shown as an example, are as follows:

Column: 265 × 110 mm ChiralPak®

Chiral Stationary Phase selector of the Amylose tris type [(S)-a methylbenzylcarbamate]

Flow rate: 570 ml/min

Detection: UV 240 nm

Temperature : Ambient temperature

These conditions are implemented on a liquid preparative chromatography apparatus.

Introduce approximately 2 g of the racemic mixture if tenatoprazole exhibiting purity higher than 99.5 %. The (-) enantiomer is identified by measuring the angle of optical rotation, which must be laevogyre. This measurement can be performed directly on the column, the product being dissolved in the solvent (acetonitrile).

Example 2 (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine

(R)-(+)-binaphthol 85 g (0.311 mol, 0.2 equivalence), ortho titanic acid isopropyl 42 g (0.148 mol, 0.1 equivalence), water 55 g (3.06 mol) and chloroform 7.5 L were stirred for 1 hour at room temperature. To the resultant, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]thio]imidazo[4,5-b]pyridine (MPI), 0.5 kg, was added and stirred for 0.5 hours at room temperature. The thus-prepared mixture was cooled to 5°C and then 70% aqueous solution of tert-butylhydroperoxide, 0.4 L (approx. 3.0 mol, 2.0 equivalence) was added and stirred for 72 hours at the same temperature as above. After the reaction endpoint was confirmed by HPLC, an aqueous solution of sodium hydroxide was added thereto to separate the aqueous layer, thus removing foreign matter. Then, the resultant was concentrated. Ethyl acetate was added to concentrated residues, which were then heated and suspended. The thus-prepared crude crystalline substances were dissolved in water and neutralized to pH 6.8 with a diluted sulfuric acid solution which was chilled with ice. Deposited crystals were filtered, dried and recrystallized by addition of ethanol to obtain (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine {(+)-TU-199}

Yield: 77%

Optical purity: 96.6%ee

Chemical purity: 94.5%

Melting point: 135°C

Optical rotation: + 184° (conditions: C=1.0, N,N-dimethylformaldehyde solution)

Ultraviolet absorption spectrum: (10µg/mL)λmax (nm): 316, 273, 206

When measurements were carried out, for a solubility of (+), (-) forms and a racemic form (\pm) of tenatoprazole in relation to water, it was found that the (+) form dissolved almost 3 times greater than the racemic body and (-) form dissolved over 2 times greater than the racemic form, exhibiting favorable physical properties in preparing drugs (refer to Table 2 below).

[Table 2]

	(+) form	(-) form	(\pm)racemic form
Solubility (water) µg/mL	93.0	74.4	34.6

CLAIMS

1. The compound (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts.
2. A method for the preparation of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, comprising column chromatography on racemic mixture.
3. The method according to claim 2, wherein the column chromatography is chiral or HPLC chromatography.
4. The method according to claim 2 or 3, wherein (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine is salfied by the action of basic mineral reagents comprising alkaline or earth-alkaline counter-ion.
5. A pharmaceutical composition comprising (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, and one more pharmaceutically acceptable excipients or substances.
6. The pharmaceutical composition according to claim 5, wherein (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine takes the form of an alikalie or earth-alkaline metal salt.
7. The pharmaceutical composition according to claim 5, wherein (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine takes the form of a sodium, potassium, lithium, magnesium or calcium salt.
8. The pharmaceutical composition according to claim 5 to 7, comprising unitary doses containing from about 10 to about 80 mg of active ingredient.
9. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies.

10. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies wherein the inhibition of acid secretion must be strong and prolonged.
11. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine for the treatment of Barrett's syndrome, atypical and oesophageal symptoms of gastro-oesophageal reflux, and digestive bleeding refractory to other proton pump inhibitors.
12. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies, gastro-oesophageal reflux, and digestive bleeding, in patients receiving multiple drug therapy.
13. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine in combination with one or more antibiotics in the manufacture of a medicinal product for the treatment of duodenal ulcer resulting from an infection by Helicobacter pylori.
14. The use of (-)-tenatoprazole, or (-)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine in the manufacture of a medicinal product displaying improved pharmacokinetic properties.
15. The compound (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts.
16. A method for the preparation of (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts, comprising that chloroform is used as a solvent and 5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} thio} imidazo-[4,5-b] pyridine is subjected to asymmetric oxidation.
17. The method according to claim 16, wherein optically active binaphthol, titanium tetraisopropoxide, water and tert-butylhydroperoxide are used.
18. A pharmaceutical composition comprising (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b]

pyridine, or one of its salts, and one more pharmaceutically acceptable excipients or substances.

19. The pharmaceutical composition according to claim 18, wherein (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine takes the form of an alkali or earth-alkaline metal salt.

20. The pharmaceutical composition according to claim 18, wherein (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine takes the form of a sodium, potassium, lithium, magnesium or calcium salt.

21. The use of (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine, or one of its salts for the treatment of digestive pathologies.

22. The use of (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine for the treatment of Barrett's syndrome, atypical and oesophageal symptoms of gastro-oesophageal reflux, and digestive bleeding refractory to other proton pump inhibitors.

23. The use of (+)-tenatoprazole, or (+)-5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridyl) methyl} sulfinyl} imidazo-[4,5-b] pyridine for the treatment of digestive pathologies, gastro-oesophageal reflux, and digestive bleeding, in patients receiving multiple drug therapy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 2004/002087

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl? C07D 471/04, A61K 31/444, A61P 1/04, 1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl? C07D 471/04, A61K 31/444, A61P 1/04, 1/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN/CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 254588 A1 (TOKYO TANABE COMPANY LIMITED)	1-5, 8, 15, 18
Y	1988.01.27 & JP 63146882 A & AU 8775628 A & ZA 8705151 A & CA 1329204 A & HU 46000 A & US 4808596 A	6-7, 16-17, 19-20
X	KAKINOKI, B., et.al, "General pharmacological properties of the New Proton Pump Inhibitor (+)-5-Methoxy-2-[(4-Methoxy-3,5-dimethylpyrid-2-yl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine", Methods and Findings in Experimental and Clinical Pharmacology (1999), 21(3), pp179-187	1-5, 8, 15, 18 6-7, 16-17, 19-20
Y	UCHIYAMA, K., et.al, "Effects of TU-199, a Novel H+, K+-ATPase Inhibitor, on Gastric Acid Secretion and Gastroduodenal Ulcers in Rats", Methods and Findings in Experimental and Clinical Pharmacology (1999), 21(2), pp115-122	1-5, 8, 15, 18 6-7, 16-17, 19-20

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18.03.2004

Date of mailing of the international search report

06.4.2004

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/002087

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	UCHIYAMA,K.,et.al, "The Long-lasting Effect of TU-199, a Novel H+,K+-ATPase Inhibitor, on Gastric Acid Secretion in Dogs", Journal of Pharmacy and Pharmacology (1999), 51(4), pp457-464	1-5,8,15,18
Y	EP 124495 A2 (Aktiobolaget Hassle) 1984.11.07 & SE A 8301182 A & PT 78191 A & NO 840772 A & FI 840851 A & DK 99584 A & JP 59-167587 A & GB 2137616 A & ZA 8401202 A & GR 79828 A & PL 246492 A & DD 221459 A & CS 8401515 A & RO 88721 A & NZ 207348 A & YU 39784 A & SU 1314953 A & PH 21352 A & IL 70985 A & US 4738974 A & BG 44538 A & CA 1264751 A & HK 13590 A & SG 1490 A & LV 5503 A & SI 8410397 A & LV 5801 A & LU 90677 A	6-7,19-20
Y	KOMATSU,N.,et.al,"Catalytic Asymmetric Oxidation of Sulfides to Sulfoxides with tert-Butyl Hydroperoxide Using Binaphthol as a Chiral Auxiliary" J. Org. Chem. (1993), 58(17), pp4529-4533	16-17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 2004 / 002087

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 9-14, 21-23
because they relate to subject matter not required to be searched by this Authority, namely:

Subject matters of these articles are "methods for treatment of the human body by therapy".
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.